

# Range of Risk Factor Levels

## Control, Mortality, and Cardiovascular Outcomes in Type 1 Diabetes Mellitus

**BACKGROUND:** Individuals with type 1 diabetes mellitus (T1DM) have a high risk of cardiovascular complications, but it is unknown to what extent fulfilling all cardiovascular treatment goals is associated with residual risk of mortality and cardiovascular outcomes in those with T1DM compared with the general population.

**METHODS:** We included all patients  $\geq 18$  years of age with T1DM who were registered in the Swedish National Diabetes Register from January 1, 1998, through December 31, 2014, a total of 33 333 patients, each matched for age and sex with 5 controls without diabetes mellitus randomly selected from the population. Patients with T1DM were categorized according to number of risk factors not at target: glycohemoglobin, blood pressure, albuminuria, smoking, and low-density lipoprotein cholesterol. Risk of all-cause mortality, acute myocardial infarction, heart failure hospitalization, and stroke was examined in relation to the number of risk factors at target.

**RESULTS:** The mean follow-up was 10.4 years in the diabetes group. Overall, 2074 of 33 333 patients with diabetes mellitus and 4141 of 166 529 controls died. Risk for all outcomes increased stepwise for each additional risk factor not at target. Adjusted hazard ratios for patients achieving all risk factor targets compared with controls were 1.31 (95% confidence interval [CI], 0.93–1.85) for all-cause mortality, 1.82 (95% CI, 1.15–2.88) for acute myocardial infarction, 1.97 (95% CI, 1.04–3.73) for heart failure hospitalization, and 1.17 (95% CI, 0.51–2.68) for stroke. The hazard ratio for patients versus controls with none of the risk factors meeting target was 7.33 (95% CI, 5.08–10.57) for all-cause mortality, 12.34 (95% CI, 7.91–19.48) for acute myocardial infarction, 15.09 (95% CI, 9.87–23.09) for heart failure hospitalization, and 12.02 (95% CI, 7.66–18.85) for stroke.

**CONCLUSIONS:** A steep-graded association exists between decreasing number of cardiovascular risk factors at target and major adverse cardiovascular outcomes among patients with T1DM. However, risks for all outcomes were numerically higher for patients with T1DM compared with controls, even when all risk factors were at target, with risk for acute myocardial infarction and heart failure hospitalization statistically significantly higher.

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## Clinical Perspective

### What Is New?

- It is unknown whether maintenance of cardiovascular risk factors at target could eliminate excess risk of mortality and cardiovascular disease associated with type 1 diabetes mellitus.
- We compared 33 333 patients with type 1 diabetes mellitus with 166 529 matched controls without type 1 diabetes mellitus.
- Patients with type 1 diabetes mellitus with 5 selected cardiovascular risk factors at target demonstrated a nonsignificant excess risk of death compared with controls.
- However, individuals with type 1 diabetes mellitus still had 82% and 97% elevated risk of myocardial infarction and heart failure, respectively, despite having all risk factors at target.
- For every incremental risk factor not at target, the excess risk of death and cardiovascular outcomes increased in a graded fashion.

### What Are the Clinical Implications?

- Achievement of current evidence-based target levels of 5 selected risk factors markedly reduces the excess risk of cardiovascular disease and may even eliminate the excess risk of mortality.

People with type 1 diabetes mellitus (T1DM) are reported to have on average a 3- to 5-fold increased risk of cardiovascular disease (CVD) and death compared with the general population, with some evidence that targeted tight glycemic control may favorably affect CVD risk.<sup>1</sup> Even with a glycohemoglobin (HbA<sub>1c</sub>) below the target level of 6.9% (52 mmol/mol), the risk of CVD and mortality is still on average twice that of the general population.<sup>2,3</sup>

The benefits of targeting multiple risk factors are now well established in type 2 diabetes mellitus.<sup>4–6</sup> Although the evidence base for such efficacy in T1DM is not nearly as robust, intensive control of glycemia, blood pressure, and low-density lipoprotein cholesterol levels has also been shown to reduce the risk of cardiovascular complications in patients with T1DM.<sup>1,7,8</sup> Although preventive strategies for cardiovascular risk mitigation similar to those for patients with type 2 diabetes mellitus are recommended for patients with T1DM, it remains unknown to what extent risk factor control may reduce the excess risk of death and CVD in T1DM.<sup>9</sup>

Our group has previously reported the excess risk of mortality and cardiovascular outcomes associated with increasing HbA<sub>1c</sub> in patients with T1DM.<sup>2,10,11</sup> In the present study, we examined the excess risk of these outcomes in patients with T1DM according to their overall CVD risk factor profile. The aim was to examine to what

extent the excess CVD risks associated with T1DM could be potentially mitigated with optimal risk factor control.

We used the Swedish National Diabetes Register to study the associations between well-recognized modifiable risk factors (HbA<sub>1c</sub>, blood pressure, low-density lipoprotein cholesterol, smoking, and albuminuria) with respect to risk for mortality and cardiovascular outcomes associated with T1DM compared with matched population controls.

## METHODS

Commercial sponsorship was not received. The ethics committee of the University of Gothenburg, Gothenburg, Sweden, approved the study. All registered patients provided written informed consent before inclusion in the cohort.

### Data Sources and Study Cohort

The Swedish National Diabetes Register was launched in 1996<sup>12</sup> and includes information on risk factors, medications, and complications of diabetes mellitus. Virtually all Swedes  $\geq 18$  years of age with T1DM are included. T1DM is defined for the National Diabetes Register on the basis of epidemiological data: treatment with insulin and a diagnosis at  $\leq 30$  years of age, which has been validated as accurate in 97% of cases, as previously reported.<sup>13,14</sup> We included patients with at least 1 registration between January 1, 1998, and December 31, 2012. For the baseline, which was the first registration in the National Diabetes Register, each patient was matched for age, sex, and county with 5 controls (without diabetes mellitus) randomly selected from the Swedish population.<sup>2</sup>

A total of 36 869 individuals with T1DM and 183 195 controls were identified. From these, we excluded individuals with T1DM who met any of the following criteria: body mass index  $< 18.5$  kg/m<sup>2</sup>, history of acute myocardial infarction, stroke, heart failure, severe chronic kidney disease (stage  $\geq 4$ ), coronary heart disease, and amputation. These patients were excluded, along with their matched controls. We excluded controls individually (ie, without excluding their matched patients) if they fulfilled the same exclusion criteria (data on body mass index or other risk factors were not available for controls). A flowchart is presented in [Figure 1 in the online-only Data Supplement](#).

### Socioeconomic Covariables

We retrieved socioeconomic data from Statistics Sweden. Country of birth was dichotomized as born in Sweden or immigrant. Income was stratified into annual quintiles. Marital categories were single, married/registered partner, divorced, or widowed. Education was categorized into  $\leq 9$  years, 10 to 12 years, and college or university degree.

### Outcomes and Coexisting Conditions

Information on coexisting conditions, outcomes, and deaths was retrieved by linking data to the nationwide Swedish Inpatient Register and the Cause of Death Register. The Swedish Inpatient Registry includes all inpatient admissions since 1987. Using the 9th and 10th revisions of the *International*

Classification of Disease (ICD), we assessed the following ICD codes: coronary heart disease (410–414 [ICD-9], I20–I25 [ICD-10], of which 410 and I21 coded acute myocardial infarction), stroke (431–434, 436 [ICD-9], I61–I64 [ICD-10]), and hospitalization for heart failure (428 [ICD-9], I50 [ICD-10]). The sensitivity and specificity for these diagnoses have been validated.<sup>15</sup> The outcomes used in this study were all-cause mortality, fatal/nonfatal acute myocardial infarction (henceforth referred to as acute myocardial infarction), hospitalization for heart failure, and fatal/nonfatal stroke (henceforth referred to as stroke).

## Variables Assessed in the National Diabetes Registry

We assessed body mass index, HbA<sub>1c</sub>, low-density lipoprotein cholesterol, total cholesterol, systolic and diastolic blood pressures, use of lipid-lowering and antihypertensive medications, smoking, physical activity (categories: never, less than once a week, once or twice a week, 3–5 times per week, or daily), and estimated glomerular filtration rate (estimated with the Modification of Diet in Renal Disease equation). Albuminuria was defined as 2 positive tests of 3 samples taken within 1 year, with microalbuminuria defined as urinary albumin-to-creatinine ratio of 3 to 30 mg/mmol or a urinary albumin clearance of 20 to 200 µg/min or 20 to 300 mg/L, and macroalbuminuria was defined as an urinary albumin-to-creatinine ratio >30 mg/mmol or a urinary albumin clearance of >200 µg/min or >300 mg/L. Definitions for risk factors are listed in Table 1.

## Definition of Risk Factor at Target and Main Objective

For the main analyses, in which we examined the risk of the outcomes in relation to the number of risk factors at target, we categorized patients with T1DM into 6 groups, defined by the number of risk factors not at target (ranging from 0–5 risk factors). Cutoffs chosen for continuous variables were based on a tradeoff between evidence base, guideline-recommended target levels, and optimizing statistical power within the observed data set. The following 5 risk factors were considered (cutoffs in parentheses): HbA<sub>1c</sub> (≥6.9% [≥53 mmol/mol]), systolic and diastolic blood pressures (either ≥140 mmHg systolic or ≥80 mmHg diastolic), albuminuria (presence of microalbuminuria or macroalbuminuria), smoking (being a smoker at study entry), and low-density lipoprotein cholesterol (>3 mmol/L).

## Statistical Methods

### Excess Risk of Outcomes According to Risk Factor Control

We used the Multivariate Imputation by Chained Equations algorithm to impute missing data for patients with diabetes mellitus. Five complete data sets were imputed.<sup>15</sup> Table 1 in the online-only Data Supplement lists the variables used in the imputation model. Table 2 and Figures 2 and 3 in the online-only Data Supplement show, along with the frequency of missing data elements, the distribution of each parameter before and after imputation.

Crude incidence rates were calculated for controls and for individuals with T1DM; for the latter group, incidence rates were calculated according to the number of risk factors at target. Crude incidence rate is expressed as the number of

events per 10 000 person-years of observation. Exact Poisson confidence intervals (CIs) were used.

Using Cox regression, we examined the risk of each outcome among individuals with T1DM compared with matched controls relation to number of risk factors not at target. We adjusted for income, education, marital status, immigrant status, age, duration of diabetes mellitus, and status at baseline with regard to history of coexisting conditions. All models were stratified on sex to allow for different underlying baseline hazards for men and women. To adjust for diabetes duration, we assigned controls to a duration of 0 years, and patients with diabetes mellitus had their duration centralized around the grand mean. Resulting hazard ratios represent the excess risk associated with T1DM at the mean duration of diabetes mellitus (18.3 years in the imputed data set). For total mortality, we included coronary heart disease, atrial fibrillation, and heart failure as comorbidities. For myocardial infarction, we included coronary heart disease, atrial fibrillation, and heart failure. For hospitalization for heart failure, we included atrial fibrillation and coronary heart disease, and for stroke, we included heart failure, atrial fibrillation, and coronary heart disease.

Calculations were performed in R (version 3.2.3) with the following packages: survival, rms, and mice (Stef van Buuren, Karin Groothuis-Oudshoorn, Alexander Robitzsch, Gerko Vink, Lisa Doove, Shahab Jolani [2015], and Multivariate Imputation by Chained Equations, R package version 2.25).

## RESULTS

### Study Population

After application of the restriction criteria, the final analysis cohort comprised 33 333 individuals with T1DM and 166 529 controls. A total of 9465 patients with diabetes mellitus had complete data on all 5 risk factors, and 23 868 individuals with diabetes mellitus had at least 1 risk factor not at target. Table 2 presents baseline characteristics and imputed data sets. Table 2 in the online-only Data Supplement shows characteristics of the participants with missing data on at least 1 risk factor. Mean

**Table 1. Definitions of Risk Factors for the Main Analyses\***

Risk Factor	Definition of Abnormal
Blood pressure	Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥80 mm Hg
LDL-C	Levels >3 mmol/L
Smoking	Being a smoker at study entry
Albuminuria	Presence of microalbuminuria or macroalbuminuria
HbA <sub>1c</sub>	≥53 mmol/mol (≥6.9%)

HbA<sub>1c</sub> indicates glycohemoglobin; and LDL-C indicates low-density lipoprotein cholesterol.

\*Patients with type 1 diabetes mellitus are stratified by the number of risk factors present.

age was 32 years, and 46% were women. Education, income, and marital status did not differ between patients and controls. Coexisting conditions were more common among patients with diabetes mellitus. The number of patients with T1DM in each risk factor category was consistent among the original and all imputed data sets. Median follow-up was 10.4 years.

### Risk for Mortality and Cardiovascular Outcomes

Figure 1A through 1D shows the number of events, event rates, and adjusted hazard ratios for all of the outcomes of interest. A total of 2074 patients with diabetes mellitus (6.2%) and 4141 controls (2.5%) died during the study period (Figure 1A). Mortality rates among patients with diabetes mellitus were lowest for those with all risk factors at target (1.58 [95% CI, 0.95–2.21] deaths per 1000 person-years). The mortality rate for controls was 2.55 (95% CI, 2.47–2.62) deaths per 1000 person-years. The adjusted mortality hazard ratio for patients with T1DM with all risk factors at target compared with their controls was 1.31 (95% CI, 0.93–1.85). The corresponding adjusted hazard ratio was 7.33 (95% CI, 5.08–10.57) for those with none of the 5 risk factors at target.

Figure 1B presents corresponding estimates for acute myocardial infarction. Incidence rates among patients with diabetes mellitus were lowest for those with all risk factors at target (0.90 [95% CI, 0.44–1.36] events per 1000 person-years). The adjusted hazard ratio for patients with T1DM versus controls with all risk factors at target was 1.82 (95% CI, 1.15–2.88). Having none of the 5 risk factors at target yielded an adjusted hazard ratio for patients with T1DM versus matched controls of 12.34 (95% CI, 7.81–19.48).

Figure 1C shows corresponding estimates for heart failure. Rates for hospitalization for heart failure among patients with diabetes mellitus were lowest for those with all risk factors at target (0.61 [95% CI, 0.19–1.03] events per 1000 person-years). The adjusted hazard ratio with respect to heart failure for patients with all risk factors at target versus matched controls was 1.97 (95% CI, 1.04–3.73). Having 5 risk factors yielded an adjusted hazard ratio for patients with diabetes mellitus compared with matched controls of 15.09 (95% CI, 9.87–23.09) for heart failure.

Estimates for stroke are presented in Figure 1D. Adjusted hazard ratios for stroke increased to 12.02 (95% CI, 7.66–18.85) for patients with none of the risk factors at target. However, patients with all risk factors at target had a hazard ratio with point estimate much closer to 1 (hazard ratio, 1.17; 95% CI, 0.51–2.68).

Men with T1DM with all risk factors at target demonstrated an adjusted hazard ratio of 1.28 (95% CI, 0.80–2.06) for all-cause mortality, whereas the corresponding hazard ratio for women was 1.32 (95% CI, 0.77–2.27; Figure 2).

### Ancillary Analyses

We carried out a subgroup analysis of the 9465 individuals with T1DM who had complete data for all variables in Table 2. This was done to compare the estimates generated from the multiple imputation models with a complete case analysis. We note that there were no material differences in cardiovascular outcomes and mortality, except for the larger CIs obtained in the complete case analysis; the risk pattern and point estimates, however, were highly comparable. [Figure IV in the online-only Data Supplement](#) provides details.

### Long-Term Trends in Risk Factor Distribution

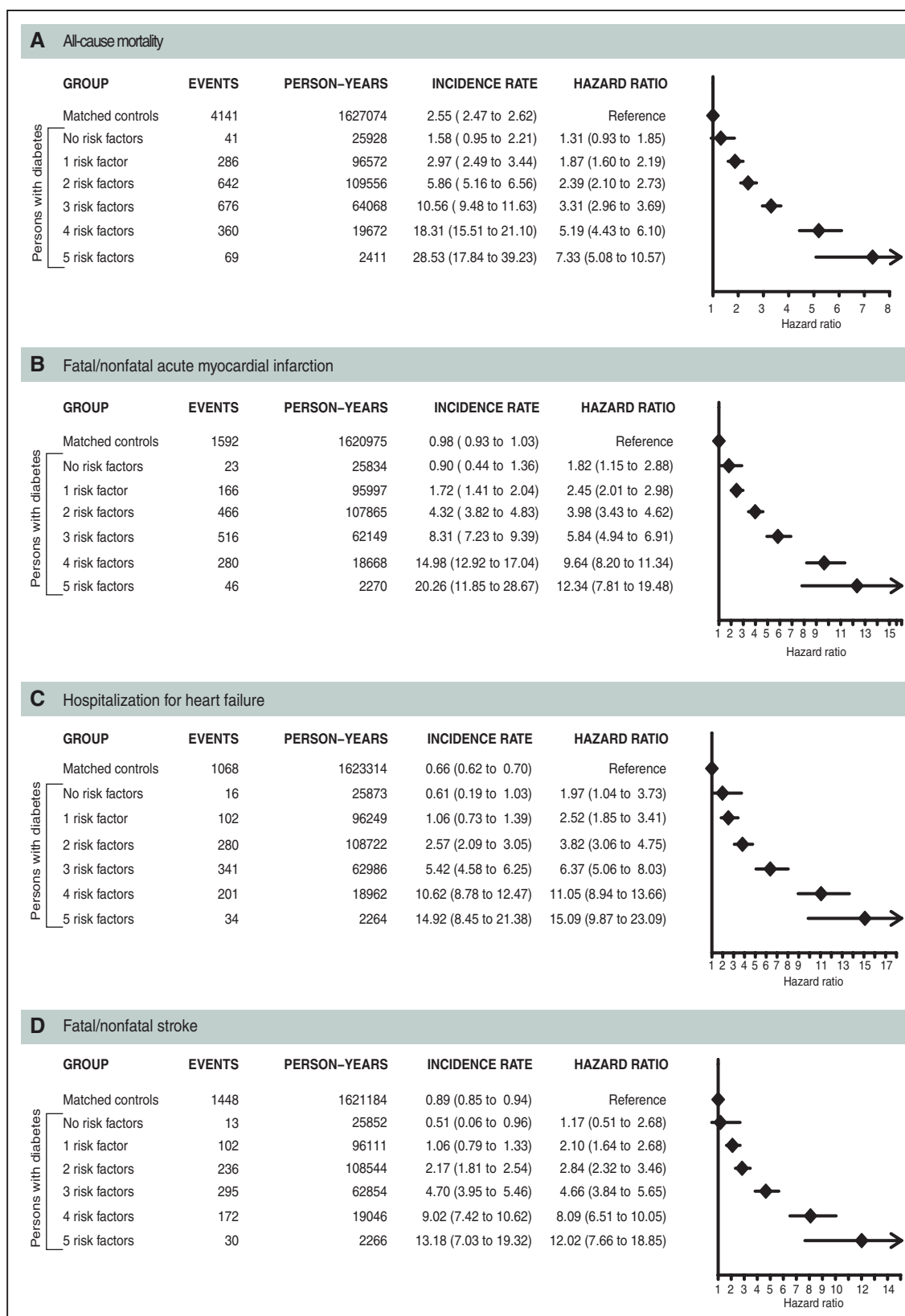
[Figure V in the online-only Data Supplement](#) shows that the proportion of patients having all risk factors at target doubled between 1998 and 2012 but still remained low at ≈11%. [Figure VI in the online-only Data Supplement](#) shows that causes of death differed between the groups studied. Dying of cancer was more common among controls, whereas cardiovascular and endocrine causes were more common among individuals with T1DM.

### DISCUSSION

This prospective observational study of 33 333 patients with T1DM and 166 529 matched controls shows that patients with T1DM with 5 selected cardiovascular risk factors at target continued to display a clear excess risk for acute myocardial infarction and heart failure compared with the general population. The excess risk for acute myocardial infarction and heart failure hospitalization remained elevated by 82% and 97%, respectively, despite all risk factors being at target. We noted an excess risk of all-cause mortality and stroke with all risk factors at target, but the excess risk was not statistically significant. It is important to note that for each risk factor not at target, we identify a steep increase in the excess risks; eg, the excess risk of death increased in a striking fashion from a 31% increase to 633% higher risk in patients with T1DM with 5 risk factors at target versus no risk factors at target (both compared with matched controls). Thus, achievement of current target levels of these risk factors appears crucial to increase longevity in patients with T1DM.

Large observational studies have recently established an excess risk for death in patients with T1DM, even when HbA<sub>1c</sub> was at target, and a decreased life expectancy in both men and women with T1DM compared with the general population.<sup>2,3</sup> Unlike type 2 diabetes mellitus, the beneficial effect of multiple risk factor control on cardiovascular outcomes in individuals with T1DM has not been studied in randomized trials.<sup>4,16</sup> This prospective study includes one of the largest cohorts of patients with T1DM with a median follow-up of 10 years and detailed





**Figure 1. Adjusted hazard ratios for all outcomes according to number of risk factors among patients with type 1 diabetes mellitus (T1DM) vs matched controls.**

**A**, The incidence rate and excess risk (hazard ratio) for all-cause mortality according to number of risk factors at target in individuals with T1DM compared with control subjects. **B**, Incidence rates and hazard ratios for acute myocardial (Continued)

risk factor and outcome data; clearly, we provide evidence that multiple risk factor control is of paramount importance in T1DM.

T1DM was associated with an incremental risk of all-cause mortality for each risk factor not at target. However, patients with all risk factors at target demonstrated a nonsignificant excess risk of death compared with matched controls. Lack of statistical significance does not equate to absence of excess risk because the point estimate (hazard ratio) was 1.31, which is well above 1.0. Lack of statistical significance could be due to lack of power (which is determined by the number of events). Thus, we fail to reject the null hypothesis, but we are obliged to redo this analysis in the future when more events are at hand.

Even with all 5 risk factors at target, patients with T1DM were at excess risk of acute myocardial infarction and heart failure. The explanations for this remain elusive, but there are some plausible explanations. The markedly elevated risk of coronary heart disease and acute myocardial infarction in T1DM has been known for decades; indeed, among all cardiovascular outcomes usually assessed, the excess risk appears to be highest for coronary heart disease and acute myocardial infarction. Hyperglycemia seems to accelerate the atherosclerotic process.<sup>1,7,9,17</sup> Note that individuals with T1DM included in our study have had hyperglycemia (even if they were below target level at inclusion) for 17 years on average. This long duration of hyperglycemia, even if well controlled, appears to be driving the excess risk of coronary artery disease, and it may not be fully compensated for by optimal risk factor control later in life.<sup>18</sup> Perhaps the same explanation is applicable to heart failure, given that recent data show that hyperglycemia may be a causal risk factor for the development of heart failure. Moreover, it is very likely that many patients in the group with all risk factors at target were actually treated (eg, with antihypertensives) to target. However, being normotensive on antihypertensive medications may not eliminate the whole risk associated with hypertension (eg, some of it will be attributable to systemic inflammation, which antihypertensives do not alleviate). The same may be applicable to dyslipidemia. Last, if we had required the use of cardioprotective medications and perhaps an insulin pump, we would have encircled an even healthier group of patients with T1DM, but we decided to not do that because we wanted to study a realistic group and because we would have lost statistical power.

It may be reasonable to treat some patients even more aggressively to further mitigate the excess risks associated with T1DM. For example, complications of

coronary artery disease predominate outcomes in patients with T1DM,<sup>1,7,17</sup> and high-dose statin treatment is both safe and effective in reducing the risk of coronary artery disease. Moreover, use of an insulin pump is a proven means to improve glycemic control and may reduce the risk of cardiovascular outcomes (including heart failure), which is why it should be considered early in the management of T1DM.<sup>19</sup>

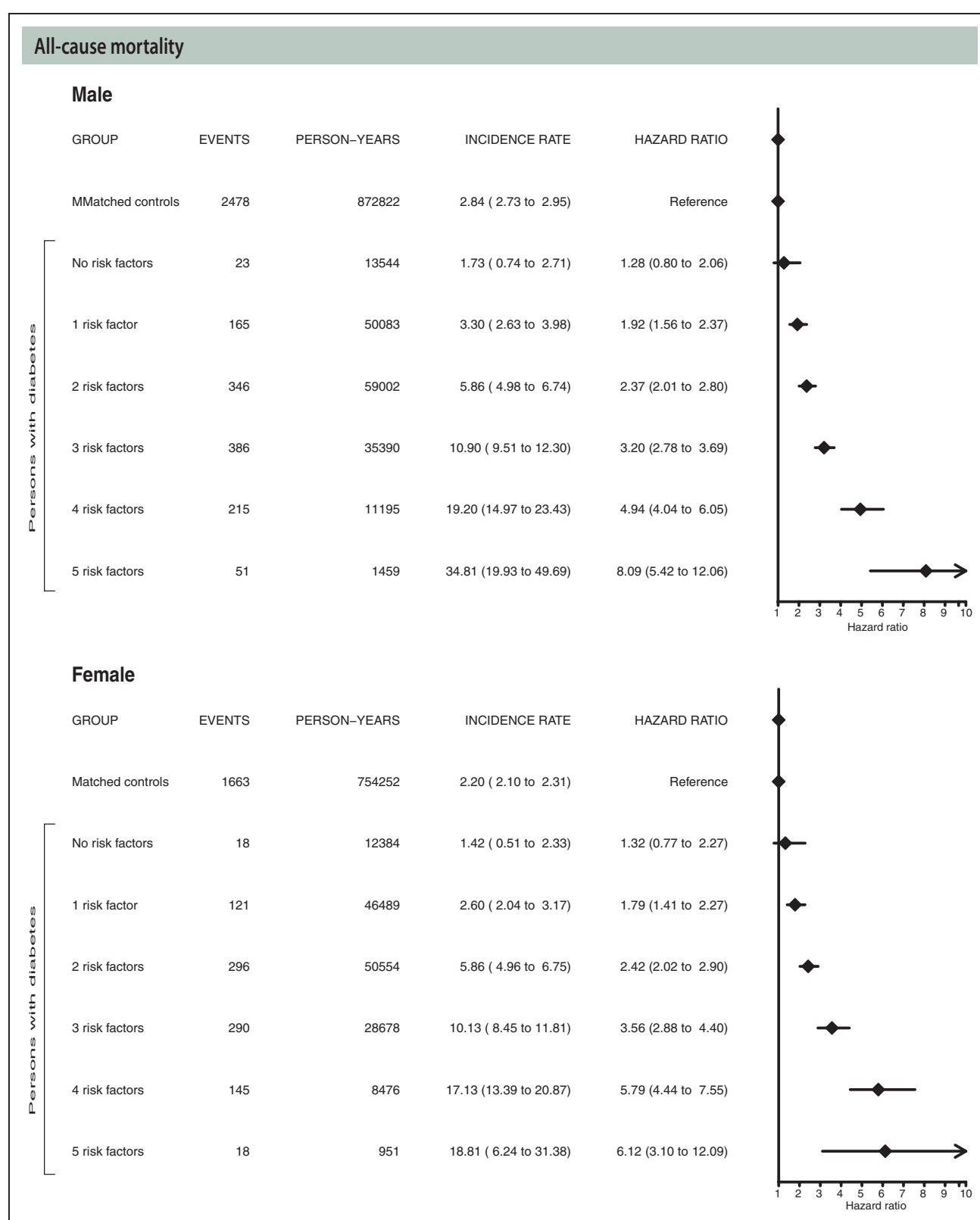
Our work therefore further underlines the importance of other cardiovascular risk factors, besides glycohemoglobin, in reducing the risk of all-cause mortality in individuals with T1DM.

Our observational study has several strengths but also some limitations. Virtually every adult patient with T1DM in Sweden was included, with information on co-existing conditions and other risk factors for all. Furthermore, matched controls were available for comparison. There are several limitations. We did not consider changes in risk factors during follow-up; we assessed only the baseline values to resemble an intention-to-treat analysis. Assessing risk factor status during follow-up would have resembled a per-protocol analysis, which we considered would bring about a high risk of complicated reverse causation. In addition, we did not distinguish patients with optimal risk factors levels *de novo* from patients medically treated to attain the optimal risk factor targets. We recognize that patients with all risk factors at target were better educated and had lower body mass index, lower blood pressure, and shorter diabetes duration than those with several risk factors not at target, and although we adjusted for several related factors, we acknowledge that residual confounding is impossible to fully overcome. The number of stroke events was limited, providing suboptimal precision of the estimates. It is also noteworthy that all point estimates (hazard ratios) were above 1.0, and inferences concerning excess risk should take into account that few events were noted among patients with all risk factors at target.

## CONCLUSIONS

Our novel findings from a national cohort suggest that the excess mortality in T1DM may be substantially reduced with stringent risk factor control. However, the excess risk of myocardial infarction and heart failure was still striking even with all risk factors at optimal levels. Our data demonstrate incremental cardiovascular risk associated with each additional classic cardiovascular risk factor not at optimal level, providing strong support for the hypothesis that aggressive multifactorial risk factor control for patients with T1DM will incrementally improve such outcomes.

**Figure 1 Continued.** infarction. **C** and **D**, Incidence rates and hazard ratios for heart failure and stroke, respectively. Crude event rates were calculated as events per 1000 patient-years. Exact Poisson 95% confidence intervals were used. Hazard ratios and incidence rates are pooled from all 5 data sets. Number of events and person-years represent the mean in the 5 data sets.



**Figure 2. Adjusted hazard ratios for all-cause mortality according to number of risk factors among male and female patients with type 1 diabetes mellitus (T1DM) vs matched controls.**

The figure displays the incidence rate and excess risk (hazard ratio) for all-cause mortality according to number of risk factors at target among male and female patients with T1DM compared with control subjects. Crude event rates were calculated as events per 1000 patient-years. Exact Poisson 95% confidence intervals were used. Hazard ratios and incidence rates are pooled from all 5 data sets. Number of events and person-years represent the mean in the 5 data sets.

**Table 2. Baseline Characteristics of Patients With Type 1 Diabetes Mellitus, Matched Controls, and the Imputed Data Sets\***

	Matched Controls	Individuals With Diabetes Mellitus With Complete Data on All 5 Risk Factors						
		Overall	No. of Risk Factors Beyond Therapeutic Targets					
			0	1	2	3	4	5
Participants, n								
Complete case data set	47 302	9465	958	3399	3237	1474	353	44
Imputed data set 1	166 529	33 333	2950	10 627	11 120	6433	1963	240
Imputed data set 2	166 529	33 333	2884	10 664	11 273	6291	1968	253
Imputed data set 3	166 529	33 333	2917	10 521	11 353	6320	1949	273
Imputed data set 4	166 529	33 333	2892	10 709	11 219	6322	1937	254
Imputed data set 5	166 529	33 333	2884	10 666	11 196	6356	1970	261
Women, n (%)	21 714 (45.9)	4345 (45.9)	435 (45.4)	1648 (48.5)	1469 (45.4)	633 (42.9)	145 (41.1)	15 (34.1)
Age, mean (SD), y	32.3 (13.7)	32.3 (13.7)	27.1 (9.7)	28.4 (11.8)	33.7 (14.4)	39.0 (14.3)	40.7 (12.8)	42.2 (9.9)
Marital status, n (%)								
Divorced	2839 (6.0)	575 (6.1)	20 (2.1)	125 (3.7)	223 (6.9)	145 (10.0)	53 (15.1)	9 (20.5)
Married	11 895 (25.3)	2204 (23.5)	153 (16.0)	627 (18.5)	848 (26.4)	463 (31.9)	100 (28.5)	13 (29.5)
Single	32 201 (68.6)	6618 (70.4)	782 (81.9)	2635 (77.8)	2138 (66.6)	843 (58.1)	198 (56.4)	22 (50.0)
Education, n (%)								
≤9 y	9103 (19.7)	1799 (19.3)	118 (12.4)	556 (16.6)	677 (21.2)	350 (24.0)	84 (24.3)	14 (31.8)
10–12 y	24 416 (52.8)	5133 (55.0)	482 (50.7)	1852 (55.3)	1746 (54.7)	818 (56.1)	208 (60.1)	27 (61.4)
College/university	12 764 (27.6)	2404 (25.7)	351 (36.9)	939 (28.1)	768 (24.1)	289 (19.8)	54 (15.6)	3 (6.8)
Income quintile, n (%)								
1 (Lowest)	8938 (18.9)	1666 (17.6)	189 (19.7)	689 (20.3)	570 (17.6)	175 (11.9)	40 (11.3)	3 (6.8)
2	8954 (18.9)	1897 (20.0)	204 (21.3)	735 (21.6)	606 (18.7)	286 (19.4)	58 (16.4)	8 (18.2)
3	9138 (19.3)	2139 (22.6)	211 (22.0)	749 (22.0)	728 (22.5)	348 (23.6)	93 (26.3)	10 (22.7)
4	9752 (20.6)	1966 (20.8)	183 (19.1)	639 (18.8)	694 (21.4)	351 (23.8)	80 (22.7)	19 (43.2)
5 (Highest)	10 507 (22.2)	1797 (19.0)	171 (17.8)	587 (17.3)	639 (19.7)	314 (21.3)	82 (23.2)	4 (9.1)
Immigrants, n (%)	6698 (14.2)	754 (8.0)	80 (8.4)	239 (7.0)	246 (7.6)	143 (9.7)	42 (11.9)	4 (9.1)
Coexisting conditions, n (%)								
Atrial fibrillation	127 (0.3)	23 (0.2)	1 (0.1)	4 (0.1)	7 (0.2)	10 (0.7)	1 (0.3)	0 (0.0)
Coronary heart disease	112 (0.2)	150 (1.6)	2 (0.2)	31 (0.9)	61 (1.9)	48 (3.3)	7 (2.0)	1 (2.3)
Heart failure	42 (0.1)	40 (0.4)	2 (0.2)	6 (0.2)	19 (0.6)	8 (0.5)	4 (1.1)	1 (2.3)
Information in the National Diabetes Register								
Duration of diabetes mellitus, mean (SD), y		17.3 (13.8)	9.5 (11.4)	13.9 (11.8)	19.0 (13.9)	23.8 (14.3)	25.9 (13.1)	27.1 (11.5)
Age at onset of diabetes mellitus, mean (SD), y		15.0 (7.7)	17.7 (7.3)	14.5 (7.6)	14.7 (7.7)	15.2 (7.8)	14.8 (8.1)	15.1 (9.0)
HbA <sub>1c</sub> , mean (SD), mmol/mol		64.8 (15.8)	45.2 (5.6)	62.9 (14.5)	68.1 (14.5)	71.6 (15.0)	74.4 (14.8)	77.6 (15.4)
LDL cholesterol, mean (SD), mg/dL		2.6 (0.8)	2.3 (0.5)	2.4 (0.6)	2.6 (0.8)	3.1 (0.9)	3.6 (1.0)	4.4 (0.7)

(Continued)



**Table 2. Continued**

	Matched Controls	Individuals With Diabetes Mellitus With Complete Data on All 5 Risk Factors						
		Overall	No. of Risk Factors Beyond Therapeutic Targets					
			0	1	2	3	4	5
Total cholesterol, mean (SD), mg/dL		4.7 (0.9)	4.2 (0.7)	4.4 (0.7)	4.7 (0.9)	5.2 (1.0)	5.8 (1.1)	6.7 (1.0)
Smoker, n (%)		1256 (13.3)	0 (0.0)	77 (2.3)	440 (13.6)	481 (32.6)	214 (60.6)	44 (100.0)
Body mass index, mean (SD), kg/m <sup>2</sup>		25.2 (4.2)	23.9 (3.4)	24.5 (3.7)	25.6 (4.4)	26.5 (4.7)	26.5 (4.6)	26.4 (5.1)
Systolic blood pressure, mean (SD), mmHg		124.0 (15.4)	114.2 (8.2)	117.4 (11.2)	127.2 (14.6)	134.1 (16.3)	139.8 (18.5)	143.2 (18.9)
Diastolic blood pressure, mean (SD), mmHg		72.7 (9.1)	67.1 (6.3)	69.2 (7.5)	74.7 (8.9)	78.0 (8.4)	80.2 (8.9)	81.7 (14.2)
No albuminuria, n (%)		8127 (85.9)	958 (100.0)	3345 (98.4)	2899 (89.6)	840 (57.0)	85 (24.1)	0 (0.0)
Microalbuminuria, n (%)		926 (9.8)	0 (0.0)	49 (1.4)	261 (8.1)	426 (28.9)	163 (46.2)	27 (61.4)
Macroalbuminuria, n (%)		412 (4.4)	0 (0.0)	5 (0.1)	77 (2.4)	208 (14.1)	105 (29.7)	17 (38.6)
eGFR, mean (SD), mL·min <sup>-1</sup> ·1.73 m <sup>-2</sup>		97.7 (25.2)	100.3 (20.5)	101.7 (22.8)	97.8 (25.2)	90.1 (28.8)	84.6 (29.0)	83.6 (32.9)
Treatment, n (%)								
Statin		1288 (14.0)	37 (3.8)	239 (7.0)	479 (14.7)	388 (26.3)	123 (34.8)	22 (50.0)
Antihypertensive		1754 (18.5)	36 (3.7)	228 (6.7)	668 (20.6)	594 (40.2)	199 (56.3)	29 (65.9)

eGFR indicates estimated glomerular filtration rate; HbA<sub>1c</sub>, glycohemoglobin; and LDL-C, low-density lipoprotein cholesterol. Survival analyses were performed on imputed data sets containing 33 333 persons with type 1 diabetes mellitus.

Concentrations for HbA<sub>1c</sub> level are based on values from the International Federation of Clinical Chemistry.

\*Baseline data for patients with diabetes mellitus (along with their matched controls) who had complete data for all 5 risk factors assessed (Table 1).

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## FOOTNOTES

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## Range of Risk Factor Levels: Control, Mortality, and Cardiovascular Outcomes in Type 1 Diabetes Mellitus

Aidin Rawshani, Araz Rawshani, Stefan Franzén, Björn Eliasson, Ann-Marie Svensson, Mervete Miftaraj, Darren K. McGuire, Naveed Sattar, Annika Rosengren and Soffia Gudbjörnsdottir

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**RANGE OF RISK FACTOR LEVELS/CONTROL,  
MORTALITY AND CARDIOVASCULAR OUTCOMES IN  
TYPE 1 DIABETES**

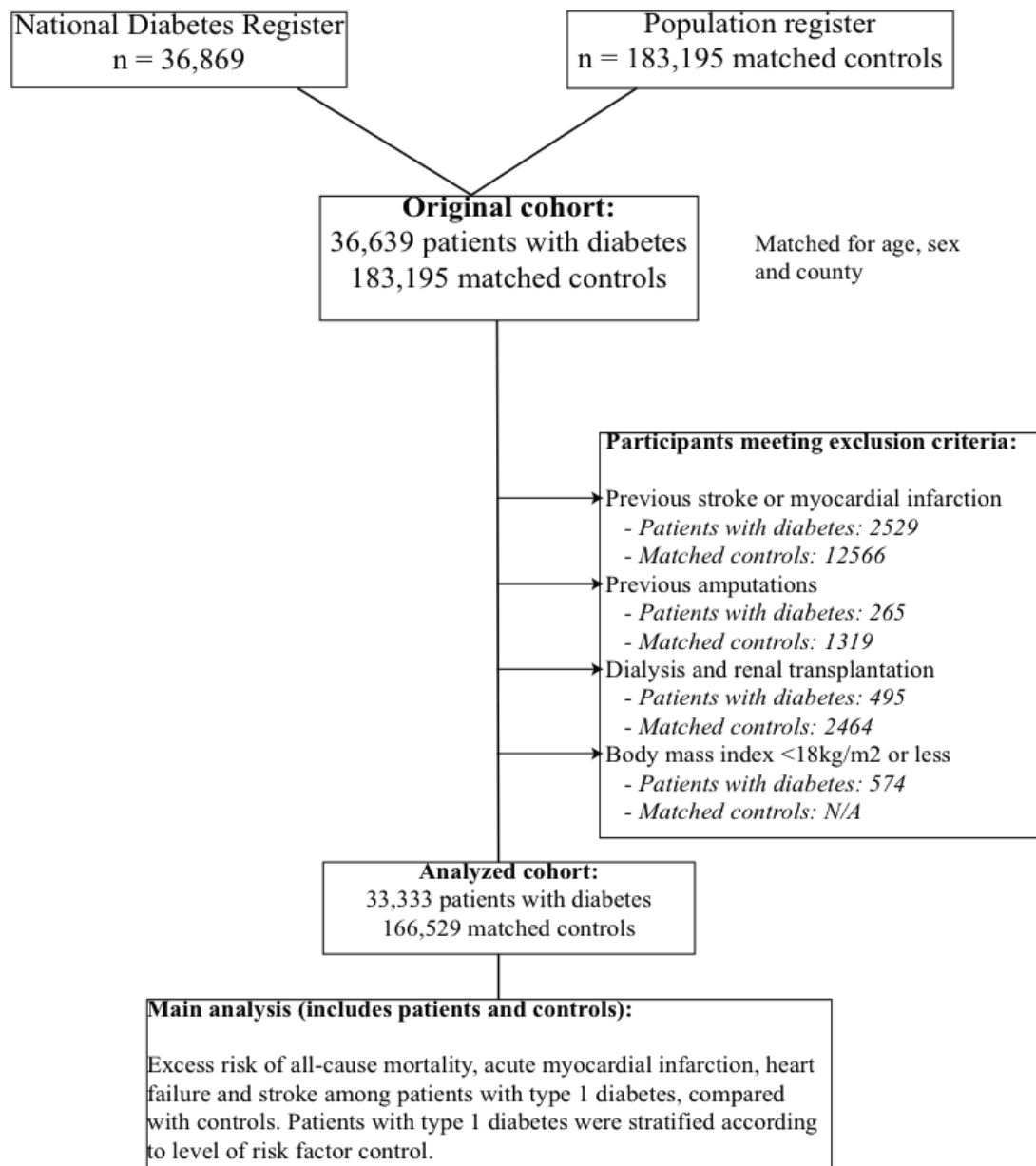
**SUPPLEMENTAL MATERIAL**

<b>Supplementary Table 1. Variables Used in the Imputation Algorithm.</b>
Age, sex, year of visit, duration of diabetes, age at onset of diabetes, smoking status, use of antihypertensive medication, use of lipid lowering medications, albuminuria, LDL cholesterol, total cholesterol, body mass index, glycated hemoglobin, systolic blood pressure, diastolic blood pressure, marital status, immigrant status, income, education, physical activity, eGFR, county, history of coronary heart disease, history of heart failure, history of atrial fibrillation, survival time for fatal/nonfatal acute myocardial infarction, outcome for fatal/nonfatal acute myocardial infarction, survival time for fatal/nonfatal stroke, outcome for fatal/nonfatal stroke, survival time for total mortality, outcome for total mortality.

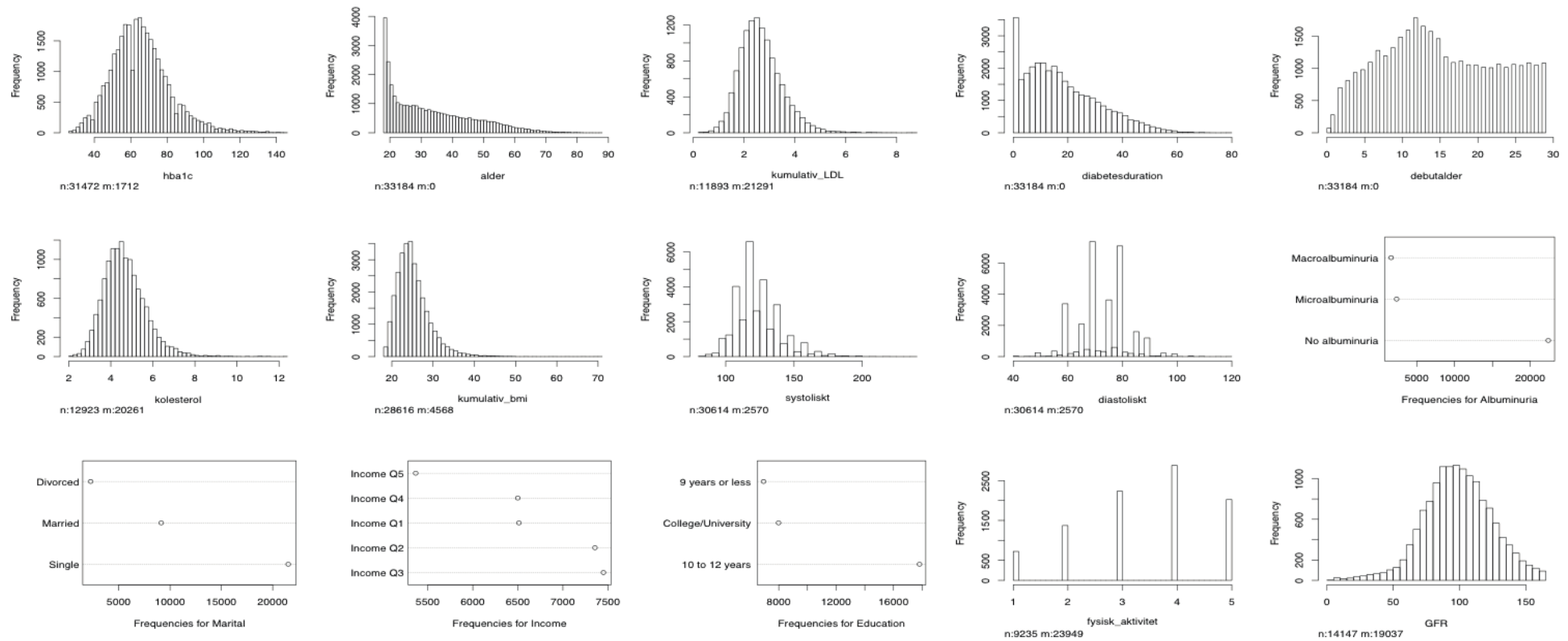


<b>Supplementary Table 2. Baseline Characteristics of Patients with Type 1 Diabetes With Missing Data.</b>		
	<b>Persons with diabetes with at least one missing risk factor</b>	<b>Persons with diabetes with no missing data</b>
n	23868	9465
Females – no. (%)	10942 (45.8)	4345 (45.9)
Age (years) – mean (SD)	34.0 (13.1)	32.3 (13.7)
<b>Marital status – no. (%)</b>		
<i>Divorced</i>	1708 (7.2)	575 (6.1)
<i>Married</i>	7009 (29.6)	2204 (23.5)
<i>Single</i>	14946 (63.2)	6618 (70.4)
<b>Education – no. (%)</b>		
<i>9 years or less</i>	5184 (22.0)	1799 (19.3)
<i>10 to 12 years</i>	12756 (54.2)	5133 (55.0)
<i>College/university</i>	5614 (23.8)	2404 (25.7)
<b>Income quintile – no. (%)</b>		
<i>Income quintile 1 (lowest)</i>	4868 (20.4)	1666 (17.6)
<i>Income quintile 2</i>	5491 (23.0)	1897 (20.0)
<i>Income quintile 3</i>	5350 (22.4)	2139 (22.6)
<i>Income quintile 4</i>	4562 (19.1)	1966 (20.8)
<i>Income quintile 5</i>	3596 (15.1)	1797 (19.0)
Immigrants – no. (%)	1578 (6.6)	754 (8.0)
<b>Coexisting conditions – no. (%)</b>		
<i>Atrial fibrillation</i>	72 (0.3)	23 (0.2)
<i>Coronary heart disease</i>	415 (1.7)	150 (1.6)
<i>Heart failure</i>	126 (0.5)	40 (0.4)
<b>Information in the National Diabetes Register</b>		
Duration of diabetes – mean (SD)	18.7 (13.4)	17.3 (13.8)
Age at onset of diabetes – mean (SD)	15.3 (7.7)	15.0 (7.7)
Glycated haemoglobin – mean (SD)	66.3 (15.9)	64.8 (15.8)
LDL cholesterol – mean (SD)	2.7 (0.8)	2.6 (0.8)

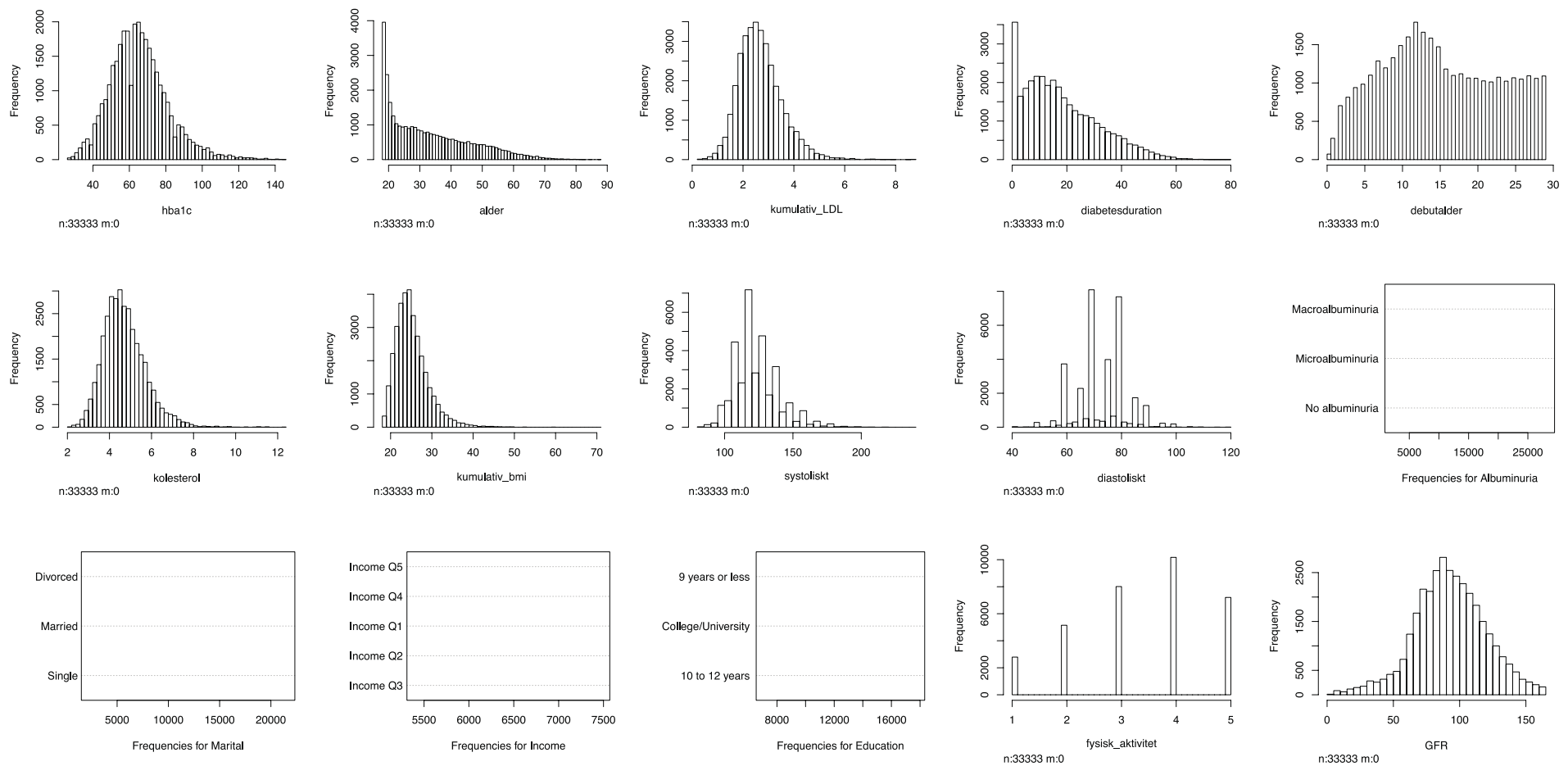
Total cholesterol – mean (SD)	4.8 (1.1)	4.7 (0.9)
Smoker – no. (%)	2968 (14.0)	1256 (13.3)
Body Mass Index – mean (SD)	25.1 (3.9)	25.2 (4.2)
Systolic blood pressure – mean (SD)	126.3 (16.4)	124.0 (15.4)
Diastolic blood pressure – mean (SD)	73.7 (9.05)	72.7 (9.1)
<b>Albuminuria – n (%)</b>		
<i>No albuminuria</i>	14336 (84.3)	8127 (85.9)
<i>Microalbuminuria</i>	1440 (8.5)	926 (9.8)
<i>Macroalbuminuria</i>	1225 (7.2)	412 (4.4)
eGFR – mean (SD)	100.7 (26.3)	97.7 (25.2)
<b>Treatment – no. (%)</b>		
<i>Statin – no (%)</i>		1288 (14.0)
<i>Antihypertensive – no (%)</i>		1754 (18.5)



**Supplementary Figure 1: Flow chart of study cohort and analyses performed.**  
Participants may fulfill more than one exclusion criteria.



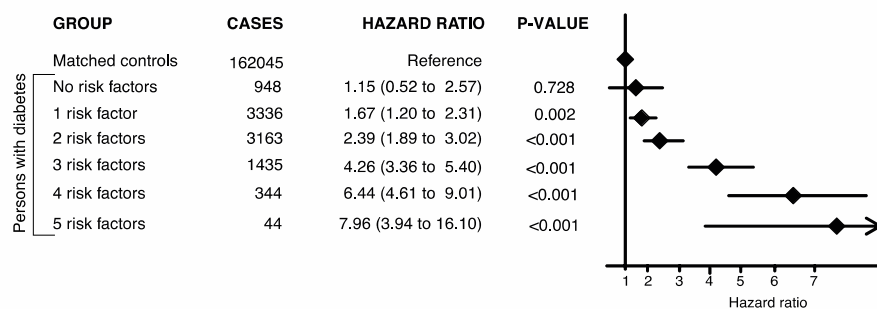
**Supplementary Figure 2. Distribution of variables used as predictors in the multiple imputation.** Variables that were included in the MICE algorithm to impute missing data for patients with T1DM. Five complete data sets were imputed. Supplemental Figure 2 shows, along with the frequency of missing data elements, the distribution of each parameter before imputation.



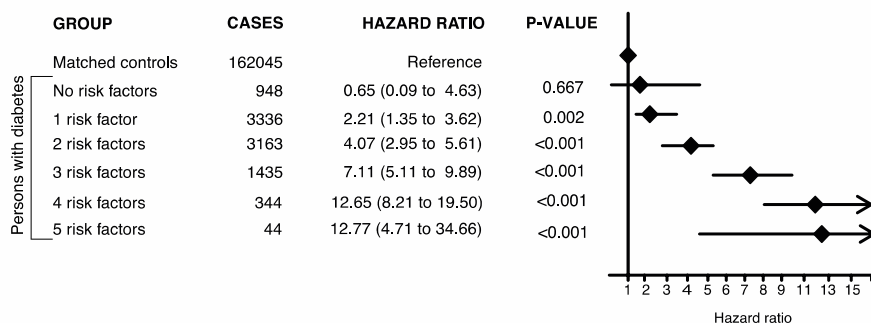
**Supplementary Figure 3. Distribution of variables after multiple imputation, showing the first imputed data set.** Variables that were included in the MICE algorithm to impute missing data for patients with diabetes. Five complete data sets were imputed. Supplemental Figure 3 shows, along with the frequency of missing data elements, the distribution of each parameter after imputation.



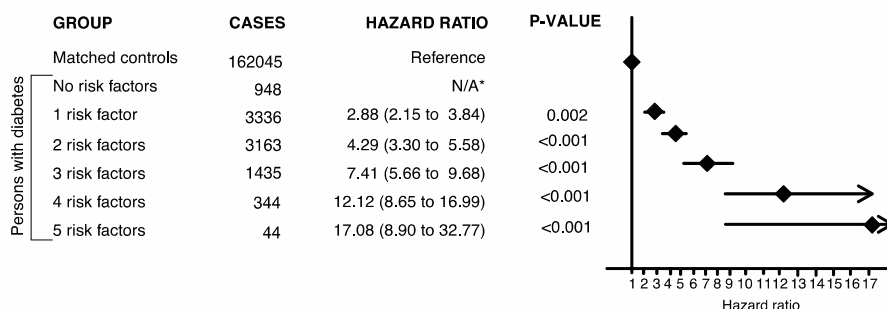
#### A All-cause mortality



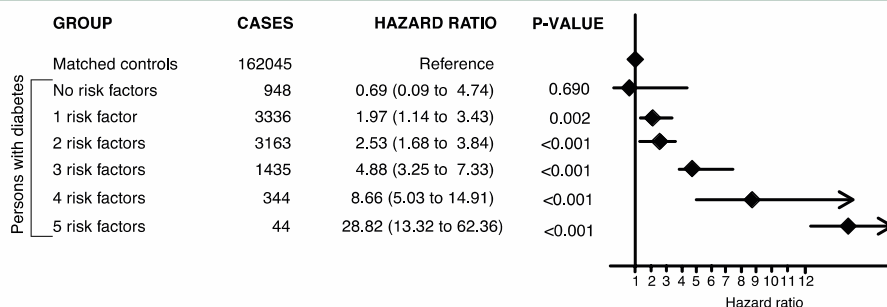
#### B Fatal/nonfatal acute myocardial infarction



#### C Hospitalization for heart failure

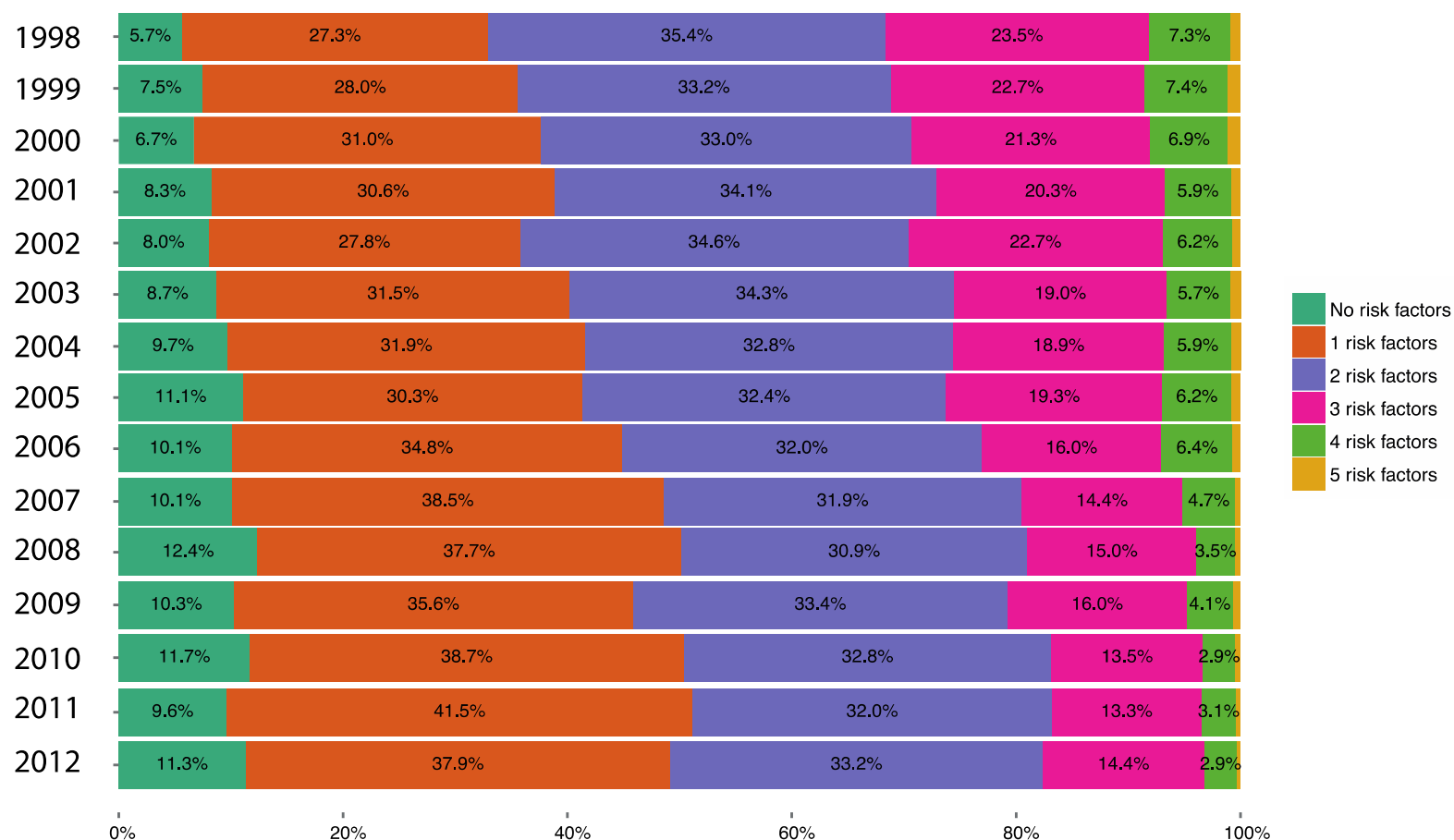


#### D Fatal/nonfatal stroke



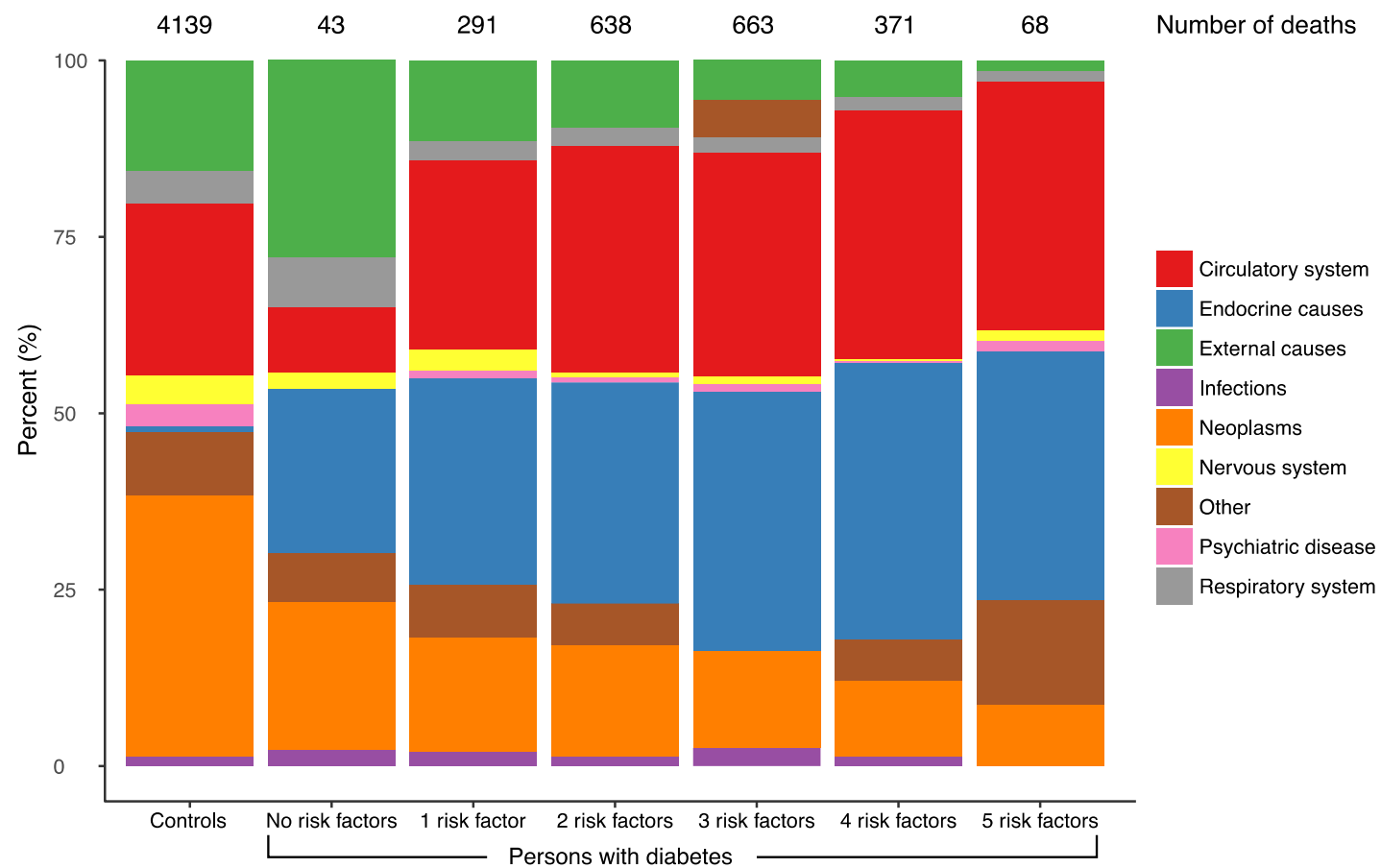
**Supplementary Figure 4. Adjusted Hazard Ratios for all Outcomes According to Number of Risk Factors Among Patients with T1DM, with Complete Data, versus Matched Controls.** Panel A. displays the hazard ratio for all-cause mortality, according to number of risk factors at target in individuals with T1DM, with complete data, as compared with controls. Panel B. displays hazard ratios for acute myocardial infarction. Panel C and D. displays hazard ratios for heart failure and stroke, respectively. Hazard ratios are pooled from all five data sets.

\* For heart failure there were zero events for the group with all risk factors at target.



**Supplementary Figure 5. Number Of Risk Factors Among Patients With T1DM According To Year.**

The y-axis displays calendar year and the x-axis displays the proportion of patients in each risk factor category.



**Supplementary Figure 6. Primary Causes of Death in the Cohort.** Primary causes of death as given in the death certificates cause of death was missing for 2 matched controls.